Remarks

Claims 1-22 were previously pending. Claim 8, 10-12, 15-22 has been canceled. Thus, with entry of this response, Claims 1-7, 9, 13-14 are pending. Claims 1, 4, 5, 13, and 14 have been amended. These amendments are supported by the specification as originally filed and no new matter is introduced. All pages referenced herein are to the published application, US Patent Application Publication No. 2006/0018956.

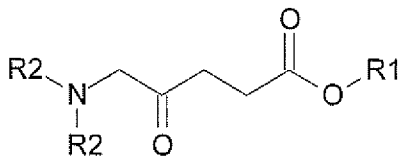
Double Patenting Rejection

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/332,547. In response, Applicants submit herewith a terminal disclaimer, disclaiming the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending Application No. 10/332,547. The fee under 37 CFR § 1.20(d) is included herewith.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-14 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Specifically, the Office Action posits that the specification does not provide a reasonably representative disclosure of any salt and any acid ester or salt of ALA. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Applicants have amended claim 1 to incorporate the limitations of prior claims 10 and 12. As a result, the ALA derivatives are limited to ALA salts and ALA esters where the ALA ester is a compound of the general formula



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wherein R1 is an unsubstituted alkyl group, and each of R2 independently from one another represents a hydrogen atom or an unsubstituted alkyl group. These claimed derivatives are sufficiently described and individualized in the original claims and in the specification (see page 5 of the specification). Moreover, these compounds are functionally similar to the compounds used in the Examples. Applicants have further amended claim 14 to be independent. Applicants note that this claim recites eight specific ALA esters derivatives. This list of derivatives does not recite a genus, but instead identifies the specific compounds by name. As such, written description is satisfied.

Rejection Under 35 U.S.C. § 103

Claims 1-6 and 8-14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 95/05813 (**WO 813**) in view of US 5,856,566 (**'566**) and further in view of WO 97/10811 (**WO 811**) and US Patent pub. 2004/0171881 (**'881**).

The Office Action first posits that **WO 813** teaches a pharmaceutical composition comprising aminolevulinic acid (ALA) applied to the skin and indicates a desire for the ALA preparation to be stable due to the normally rapid degradation of ALA. The Office Action recognized that **WO 813** does not teach crystalline ALA having a mean particle size between 20 and 200 μm as recited in claim 1 or a mean particle size between 30 and 190 μm, or between 90 and 160 μm as recited in claims 4 and 5, respectively. In recognition of this deficiency in the teachings of **WO 813**, the Office Action alleges that "[i]n order to overcome the degradation problem, **'566** suggests employing micronized crystals of ALA."

The Office Action further attempts to demonstrate a motivation in **'881** and **WO 811** for use of nano-crystaline formulations. Specifically, the Office Action alleges that "'**881** discloses that nano crystalline formulations typically afford greater bioavailability of drug compounds (see paragraph [1426]) and **WO 811** discloses the benefit of enhancing solubility and use of nano particles in photodynamic therapy (abstract title and page 3, first paragraph)."

The Office Action then alleges that it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to employ crystalline ALA or derivatives thereof in the transdermal compositions of **WO 813** since both **'566** and **WO 813** desired a stable preparation that does not degrade. According to the Office Action, **'566** suggests solving this problem by using crystals of ALA having sizes in micrometers, which **'566** allegedly teaches are stable in addition to being sterile. The Office Action further alleges that it would have been obvious to one of an ordinary skill in the art at the time of the instant invention to optimize the particle size of ALA/ALA derivatives as disclosed by **WO 813** based inter alia on the motivation provided by **'881** and **WO 811** to use nano crystalline formulations to afford greater bioavailability of drug compounds.

Applicants respectfully traverse this rejection. Even if the instant rejection is properly reasoned, the conclusion is based on faulty premises. Specifically, the Examiner has mischaracterized what the cited references fairly teach in order to fit the facts to the rejection.

First, the Office Action erroneously alleges that **'566** teaches the use of micronized crystals of ALA"[i]n order to overcome the degradation problem." While it is true that **'566** has as its objective to provide ALA that does not suffer from extreme degradation, the solution provided in **'566** is not micronization as the Office Action claims. Rather, as alluded to in the title of the patent, **'566** teaches that sterilization—not micronization—improves the stability of ALA for storage. Specifially, **'566** discloses the use of gamma-irradiation to "color" ALA for the purposes of

sterilization (column 2, lines 59-64). Moreover, as noted in column 4, lines 50-54, it was surprising to the patentees that the gamma irradiated material was stable for extended periods of time when stored in sealed bottles in which it was irradiated. In contrast, as noted in the paragraph bridging columns 4 and 5, the micronization disclosed in **'566** was not for the purposes of increasing stability, but rather an effort to evaluate the color intensity created by the gamma irradiation for different crystalline forms. See also column 10, lines 15-17, wherein it states that the micronization was "to determine if further reducing the crystalline size would have any effect on the color of the irradiated ALA." Significantly, there is no indication in **'566** that the micronized ALA was more stable than non-micronized ALA. Therefore, **'566** does not fairly teach the micronization of ALA to increase stability as erroneously posited in the Office Action.

Perhaps more significantly, **'566** does not teach the use of crystalline ALA in a dermal application system. Instead, **'566** teaches only the storage of ALA in crystalline form. For use in photodynamic therapy, **'566** discloses administration of a solution of ALA derived from the colored ALA crystals disclosed therein (column 3, lines 2-25). In fact, none of the cited references suggest the use of ALA in a dermal application system in its crystalline form. The Examiner is using impermissible hindsight to find motivation for this use in references that only teach the storage of ALA in crystalline form.

Thus, the skilled artisan would not have been motivated to use micronized and crystalline ALA/ ALA derivatives in a dermal application system based on the combination of **WO 813** and **'566**.

Second, the Office Action erroneously applies the teachings of **'881** and **WO 811** to the instant claims. As noted above, the combination of **WO 813** and **'566** do not teach or suggest the suspension of crystalline ALA/ ALA derivatives at the clamed sizes in a polymer matrix, and the

Office Action erroneously attempts to correct these deficiencies by applying the teachings of **WO 811** and **'881** to ALA.

WO 811 details a methodology to solubilize zinc phthalocyanine complex in an aqueous solution using nanoparticles, because zinc phthalocyanine complex is "characterized by extremely low water solubility and insolubility in almost all organic solvents." **WO 811** solves the problem of poor water solubility of zinc phthalocyanine complexes by addition of a polymer support which—mixed with the active agent—is provided in the form of nanoparticles and can be dissolved, which is necessary for intravenous administration. However, in the context of the present invention, ALA/ ALA derivative is suspended in a transdermal matrix and not dissolved for intravenous administration. There are no problems with solubility of ALA/ALA derivatives in this context One of skill in the art would thus not rely on this reference to correct the deficiencies of **WO 813** and **'566**, since the nanoparticles of **WO 811** were described to solve a problem not relevant to the ALA transdermal system of **WO 813**.

The **'881** suffers a similar defect. U.S. Pat. Nos: 5,145,684 and 6,045,829, which were cited by **'881** for preparations of nano-crystal dispersion formulations, also use nano-crystals to solve the problem of poor gastrointestinal absorption of a poorly water soluble drug by increasing the drug's surface area with "a surface modifier adsorbed on the surface" (5,145,684) or "a cellulosic surface stabilizer" (6,045,829). As patent 5,145,684 states:

> Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/ml, tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, *poorly water soluble drugs* tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances. It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions.

Again, there are no problems with solubility of ALA/ ALA derivative in the context of the present invention. Thus, the nanoparticles of **'881,** like **WO 811,** were described to solve a problem not relevant to the ALA transdermal system of **WO 813**. There is therefore no reason in the prior art to combine **WO 811** and/or **'881** with **WO 813** and **'566.**

Finally, in response to Applicants' arguments that the size range of nanoparticles (0.01 to 1 μm) is well below that of the presently claimed ALA derivative crystals (20 to 200 μm), the Office Action erroneously asserted that the claims are directed to "mean diameter" and "not the exact size of ALA crystals. This assertion is based on a misunderstanding of the term. The term does not refer to the mean of all of the particles, which could thus include both nanoparticles and macroparticles and in fact very few if any microparticles. Instead, the term refers to the mean of each particle. Crystals by nature have non-uniform shapes. It is therefore impossible to refer to a specific diameter of a crystalline particle. Instead, the claims refer to "mean diameter" to take into account this non-uniformity. Thus, the claimed particle sizes do not read on nanoparticles. Notably, since the claim recites "wherein a substantial amount of the crystals of the ALA derivative have a mean diameter of 20 μm to 200 μm," the claimed dermal application system can (and likely will) have some nanoparticles present within. Even so, a substantial amount of the crystals will be microparticles that achieve a non-obvious advantage over the prior art method of using dissolved ALA.

As the references cited in the Office Action do not teach the elements of the claimed dermal application system as asserted, the rejection is improper and cannot stand. Applicants therefore respectfully request the withdrawal of the instant rejection and allowance of the claims.

Conclusions

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to

directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment authorizing payment in the amount of $1,650.00, representing $1,175.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(5) for a Five Month Extension of Time, $405.00 for the fee for a small entity under 37 C.F.R. § 1.17(e), and $70.00 for the fee for a small entity under 37 C.F.R. § 1.20(d), is hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1513.

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Respectfully submitted,

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In accordance with 37 C.F.R. § 1.8, I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below

P. Brian Giles, Ph.D

12-18-2009
Date